Introduction of 20-Keto Side Chains in 17-Oxosteroids: Wittig-Horner-Emmons Reactions of (*E*)-17-[(Diethylphosphono)isocyanomethylene]-3-methoxyandrosta-3,5-diene[1]

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The synthesis is described of a series of polyfunctional unsaturated $\Delta^{16,20}$-20-isocyanosteroids **5a-f** by the Wittig-Horner-Emmons reaction of (*E*)-17-[(diethylphosphono)isocyanomethylene] steroid **4** with several aldehydes and with acetone. Hydrolysis of the isocyanosteroids **5a-f** with dilute sulfuric acid gave Δ^{16}-20-ketosteroids **6a-f** in high yield. Hydrolysis of **5a** was also possible under neutral conditions, *via* the intermediate $\Delta^{16,20}$-20-isocyanatosteroid **7a**, leading to A-ring protected 16-dehydroprogesterone **8a**. The Wittig-Horner-Emmons reaction, together with the described hydrolyses, provides a new method for the introduction of steroid side chains. The method is particularly suited for side chains of different size, structure, and functionality.

Microbiological degradation of the side chain of vegetable sterols, such as β-sitosterol, provides an efficient method of manufacturing 17-oxosteroids.[2] Therefore, 17-oxosteroids are ideal starting materials for synthetic conversion into more complex derivatives. This situation has led to a significant increase over the last two decades in efforts to introduce specific side chains at C17, for example, the side chains of corticosteroids and 25-hydroxycholesterol, in precursors such as the dienol ether of androst-4-ene-3,17-dione (**1**).[3] Often, classical approaches (Wittig-type reactions,[3b] aldol-type condensations,[3b] Claisen and Cope rearrangements,[4] ene reactions[5]) are combined with newer methods, based on organopalladium[6] and organocopper chemistry,[7] to arrive at side chains with the desired composition of functionality and stereochemistry. By such methods, 17-oxosteroids have been converted into several naturally occuring compounds, *inter alia* 20-ketosteroids,[8] Δ^{16}-20-ketosteroids and corticosteroids,[9,10] and 25-hydroxycholesterol.[11] 25-Hydroxycholesterol is an important intermediate in the synthesis of 1α,25-dihydroxyvitamin D_3,[12] which recently has attracted interest by its ability to control cellular differentiation and proliferation.[13]

The structure of the C17 side chain also determines the physiological activity of steroid compounds, which are of prime importance in medicine. This explains the continuing interest in the development of generally applicable methods for constructing steroid side chains, especially of methods that allow the introduction of side chains with additional functionality. Recently, we have described the synthesis of (*E*)-17-[(diethylphosphono)isocyanomethylene] steroid **4** (and analogs) from 17-oxosteroids such as **1**[14] and diethyl (isocyanomethyl)phosphonate (**2**), both of which are commercially available. Previously, we have used compound **4** as intermediates in the synthesis of Δ^{16}-20-ketosteroids and progesterone, through alkylation and hydrolysis.[1a] In the present paper, we will show that compound **4** is an attractive intermediate also for the introduction of C17 steroid side chains using Wittig-Horner-Emmons methodology (Scheme I).

Wittig-type reactions have been successfully applied in steroid chemistry: (1) in the preparation of intermediates for the synthesis of steroids *via* biomimetic polyene cyclizations,[16] (2) in the total synthesis of vitamin D_3 and analogs by coupling of the Windaus-Grundmann ketone[17]

(1) This paper is part 5 of the series Chemistry of Phosphorylmethyl Isocyanides. Previous papers are: (a) Stoelwinder, J.; van Zoest, W. J.; van Leusen, A. M. *J. Org. Chem.* **1992**, *57*, 2249. (b) Stoelwinder, J.; van Leusen, A. M. *Synthesis* **1990**, 568. (c) Moskal, J.; van Leusen, A. M. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 137. (d) Moskal, J.; van Leusen, A. M. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 141. These papers are to be considered parts 4, 3, 2, and 1, respectively, of this series.

(2) (a) Wovcha, M. G.; Antosz, F. J.; Knight, J. C.; Kominek, L. A.; Pyke, T. R. *Biochim. Biophys. Acta* **1978**, *539*, 308. (b) Marsheck, W. J.; Kraychy, S.; Muir, R. D. *Appl. Microbiol.* **1972**, *23*, 72.

(3) Reviews: (a) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. (b) Redpath, J.; Zeelen, F. J. *Chem. Soc. Rev.* **1983**, *12*, 75. (c) Nitta, I.; Hiroaki, U. *J. Synth. Org. Chem. Jpn.* **1987**, *45*, 445. (d) Turner, A. B. *Nat. Prod. Rep.* **1992**, *9*, 37. (e) Turner, A. B. *Nat. Prod. Rep.* **1991**, *8*, 17.

(4) (a) Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172. (b) Tanabe, M.; Hayashi, K. *J. Am. Chem. Soc.* **1980**, *102*, 862.

(5) (a) Dauben, W. G.; Brookhart, T. *J. Am. Chem. Soc.* **1981**, *103*, 237. (b) Batcho, A. D.; Berger, D. E.; Uskoković, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1293. (c) Batcho, A. D.; Berger, D. E.; Dauvoust, S. G.; Wovkulich, P. M.; Uskoković, M. R. *Helv. Chim. Acta* **1981**, *64*, 1682.

(6) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1981**, *100*, 3435. (b) Trost B. M.; Matsumura, Y. *J. Org. Chem.* **1977**, *42*, 2036. (c) Temple, J. S.; Schwartz, J. *J. Am. Chem. Soc.* **1980**, *102*, 7381. (d) Reidiker, M.; Schwartz, J. *Tetrahedron Lett.* **1981**, *22*, 4655.

(7) Marino, J. P.; Abe, H. *J. Am. Chem. Soc.* **1981**, *103*, 2907.

(8) (a) Danishefsky, S.; Nagasawa, K.; Wang, N. *J. Org. Chem.* **1975**, *13*, 1989. (b) van Leusen, D.; van Leusen, A. M. *Synthesis* **1991**, 531.

(9) (a) van Leusen, D.; van Echten, E.; van Leusen, A. M. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 469. (c) van Leusen, A. M.; van Leusen, D. U.S. Patent US 4 551 728, 1985. (d) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Nouv. J. Chim.* **1982**, *6*, 295. (e) Wroble, R. R.; Watt, D. S. *J. Org. Chem.* **1976**, *41*, 2939.

(10) (a) Carruthers, N. I.; Garshasb, S.; McPhail, A. T. *J Org. Chem.* **1992**, *57*, 961. (b) Livingston, D. A.; Petre, J. E.; Bergh, C. L. *J. Am. Chem. Soc.* **1990**, *112*, 6449 and references cited therein. (c) Barton, D. H. R.; Zard, S. Z. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2191. (d) van Leusen, A. M.; van Leusen, D. U.S. Patent US 4 548 749, 1985. (e) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. U.K. Patent GB 2 079 756 B, 1984. (f) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1981**, 774. (g) Neef, G.; Eder, U.; Seeger, A.; Wiechert, R. *Chem. Ber.* **1980**, *113*, 1184.

(11) (a) Wicha, J.; Bai, K. *J. Chem. Soc., Chem. Commun.* **1975**, 968. (b) Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1982**, *23*, 2077.

(12) Kametani, T.; Furuyama, H. *Med. Chem. Rev.* **1987**, *7*, 147.

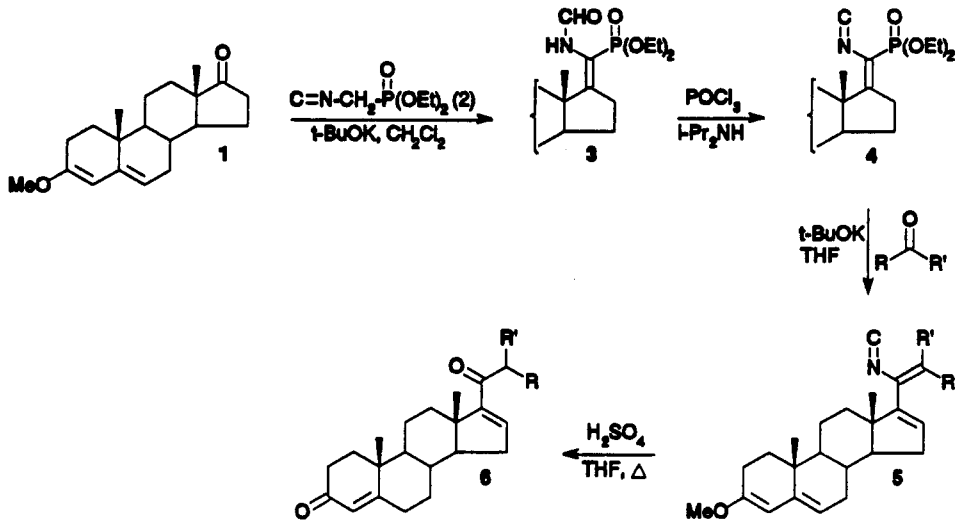
(13) (a) Yamada, S.; Yamamoto, K.; Naito, H.; Suzuki, T.; Ohmori, M.; Takayama, H.; Shiina, Y.; Miyaura, C.; Tanaka, H.; Abe, E.; Suda, T.; Matsunaga, I.; Nishii, Y. *J. Med. Chem.* **1985**, *22*, 1148. (b) Ostrem, V. K.; DeLuca, H. F. *Steroids* **1987**, *49*, 73.

(14) 3-Methoxyandrosta-3,5-dien-17-one (**1**) is readily obtained from commercially available androst-4-ene-3,17-dione by reaction with trimethyl orthoformate.[15] The dienol ether protection of the 3-oxo group is needed to direct the reaction of diethyl (isocyanomethyl)phosphonate (**2**) and **3** to the 17-oxo group at C17 exclusively.

(15) Nussbaum, A. I.; Yuan, E.; Dinçer, D.; Oliveto, E. P. *J. Org. Chem.* **1961**, *26*, 3925.

0022-3263/93/1958-3687$04.00/0

Scheme I[a,b]

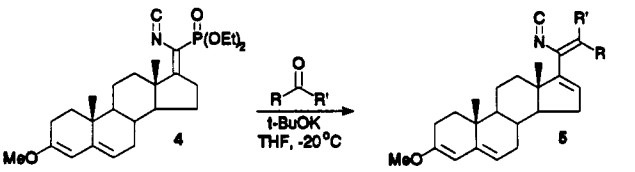


[a] For specification of R and R', see Table I. [b] For the function of the dienol methyl ether group in 1, see ref 14.

with phosphorus substituted A-ring synthons,[18] and (3) in side chain construction from steroidal aldehydes[19] and phosphorus-containing side chain precursors.[20] The reversed approach in relation to (3), in which the phosphorus fragment is attached to steroid derivatives at C20, as in **4**, and the side chain precursor is an aldehyde, has not previously been reported to the best of our knowledge.[21] The availability of a large variety of side chain precursors forms an attractive aspect of this new approach.

Recently, we have shown that **4** is easily deprotonated at C16 and that the resulting allylic anion is methylated exclusively at C20.[1a] It now appears that the same allylic anion undergoes Wittig–Horner–Emmons reactions—also at C20—with a series of aldehydes to give $\Delta^{16,20}$-20-isocyanosteroids **5a,b,c,e,f** in good yields (Table I). The reaction applies to ketones also. Reaction with acetone gave comparable results (**5d**, Table I, entry 4).[22] Entries 5 and 6 show that good results were obtained also with two bifunctional side chain precursors: ethyl 4-oxobutanoate and (*E*)-2-hexenal. The first of these reactions (entry 5) provides **5e** with a 21-norcholestane side chain, with a carboxylate group at the C24 position, which forms a useful handle to introduce the important hydroxy group of 25-hydroxycholestanes.[23]

Table I. $\Delta^{16,20}$-20-Isocyanosteroids 5a–f Prepared by a Wittig–Horner–Emmons Reaction of 4 with Aldehydes and with Acetone



entry	R	R'	compd	yield (%)	*E*/*Z*[a]	mp (°C)
1	H	H	**5a**	96		152–153
2	H	CH_3	**5b**	96	14/86	152–156[b,c]
3	H	$(CH_2)_3CH_3$	**5c**	81	7/93	91–101[b]
4	CH_3	CH_3	**5d**	87		158–159
5	H	$(CH_2)_2CO_2Et$	**5e**	71	13/87	104–111[b]
6	H	CH=CH-Pr(n)	**5f**	83	9/91	120–125[b,c]

[a] The *E*,*Z*-ratio of **5b,c,e**, and **f** was determined by ^{1}H NMR (see Experimental Section); the predominant isomer tentatively assigned *Z*, see text. [b] Mp of analytically pure (*Z*)-**5b,c**, and **f**, obtained by two crystallizations from the *E*,*Z* mixture. [c] Mp with decomposition.

The overall result of the successive reactions from **1** to **5** (Scheme I) is the conversion of the 17-oxo group of androst-4-ene-3,17-dione into α,β-unsaturated isocyanides **5a-f**, with an additional double bond at C16,C17. Compounds **5b, c, e**, and **f** were obtained as mixtures of *E*- and *Z*-isomers, the ratio of which was determined by ^{1}H NMR (Table I, and Experimental Section). The prevailing isomers have been obtained in a pure state by crystallization and were assigned the sterically favored *Z* configuration. These assignments, however, are tentative. Extensive NOESY measurements with (*Z*)-**5b** and (*E*,*Z*)-**5b**, as well as (*E*,*Z*)-**5c**, have provided no support for either assignment, not for the C17,C20 cisoid conformation, as depicted, or for the transoid conformation. In the case of **5b** (both for *Z* and *E*), only a nonrelevant cross coupling was observed between C(21)H and C(22)H. Crystals suited for X-ray analysis were not obtained. The *E*,*Z* configu-

(16) (a) Gravestock, M. B.; Johnson, W. S.; McCarry, B. E.; Parry, R. J.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4274. (b) Johnson, W. S.; DuBois, G. E. *J. Am. Chem. Soc.* **1976**, *98*, 1038.

(17) (a) Windaus, A.; Grundmann, W. *Liebigs Ann. Chem.* **1936**, *524*, 295. (b) Inhoffen, H. H.; Quinkert, G.; Schütz, S.; Kampe, D.; Domagk, G. F. *Chem. Ber.* **1957**, *90*, 664.

(18) (a) Nemoto, H.; Suzuki, K.; Tsubuki, M.; Minemura, K.; Fukumoto, K.; Furuyama, H.; Kametani, T. *Tetrahedron* **1983**, *39*, 1123. (b) Lythgoe, B.; Morgan, T. A.; Nambudiry, M. E. N.; Tideswell, J.; Wright, P. W. *J. Chem. Soc., Perkin Trans. 1* **1978**, 590.

(19) (a) Sheikh, Y. M.; Djerassi, C. *Steroids* **1975**, *26*, 129. (b) Barton, D. H. R.; Davies, P. J.; Kempe, U. M.; McGaritty, J. F.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1231. (c) Schmit, J. P.; Piraux, M.; Pilette, J. F. *J. Org. Chem.* **1975**, *40*, 1586.

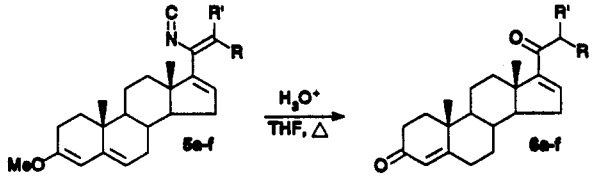
(20) Gosney, I.; Rowley, A. G. In *Organophosphorus Reagents in Organic Synthesis*, Cadogan, J. I. G., Ed.; Academic Press: London, 1979; pp 137–142.

(21) (a) In one related example a C22 phosphorus-bearing steroid (i.e., [(20*S*)-6β-methoxy-20-methyl-3α,5α-cyclopregnan-22-yl]triphenylphosphonium iodide) was reacted previously with (*R*)- and (*S*)-2,2,4-trimethyl-1,3-dioxolane-4-acetaldehyde in the synthesis of vitamin D_3 metabolites: Barner, R.; Hübscher, J.; Daly, J. J.; Schönholzer, P. *Helv. Chim. Acta* **1981**, *64*, 915. Barner, R.; Hubscher, J. Eur. Patent EP 19 0 59, 1980. (b) For further examples of reactions with a C24 phosphorus bearing steroid and several ketones, see: Herz, J. E.; Cruz Montalvo, S. *Org. Prep. Proceed. Int.* **1975**, *7*, 16. Herz, J. E.; Cruz Montalvo, S. *Steroids* **1971**, *17*, 649.

(22) Since the target 20-ketosteroids do not usually carry two alkyl or aryl, alkyl substituents at C21, we have worked out in detail only one example of a reaction of **4** with a ketone (acetone, Table I, entry 4). Nevertheless, even less reactive ketones as acetophenone and pinacolone do react with **4**, albeit in lower yields.

(23) Reaction of MeMgX or MeLi with an ester function at C24 is known to give 25-hydroxycholestane, as has been shown by several research groups: (a) Pearlman, W. H. *J. Am. Chem. Soc.* **1947**, *69*, 1475. (b) Lettré, H.; Egle, A.; von Jena, J.; Mathes, K. *Liebigs Ann. Chem.* **1967**, *708*, 224. (c) Cohen, B. I.; Tint, G. S.; Kuramoto, T.; Mosbach, E. H. *Steroids* **1975**, *25*, 365.

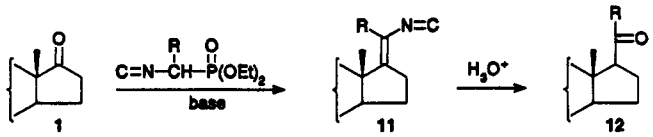
Table II. Δ^{16}-20-Ketosteroids 6a–f Prepared by Acid Hydrolysis of $\Delta^{16,20}$-20-Isocyanosteroids 5a–f



entry	R	R′	compd[a]	yield (%)	$[\alpha]^{20}_D$	mp (°C)
1	H	H	6a	93	+156°	186–187[b]
2	H	CH_3	6b	96	+168°	158–159[c]
3	H	$(CH_2)_3CH_3$	6c	85	+130°	120–121
4	CH_3	CH_3	6d	93	+145°	145–147
5	H	$(CH_2)_2CO_2Et$	6e	43[d]	+126°	97–98
6	H	CH=CH-Pr(n)	6f	89	+126°	98–100

[a] The 3,5-dienol ether protection group of compounds 5a–f was hydrolyzed concomitantly to the 4-en-3-one function. [b] Lit.[31] mp 186–188 °C, $[\alpha]^{20}_D$ +155° (c 1, EtOH). [c] Lit.[27] mp 159–160 °C, $[\alpha]^{20}_D$ +168° (c 1, CH_2Cl_2). [d] Low yield due to partial hydrolysis of 24-ethyl ester.

Scheme II



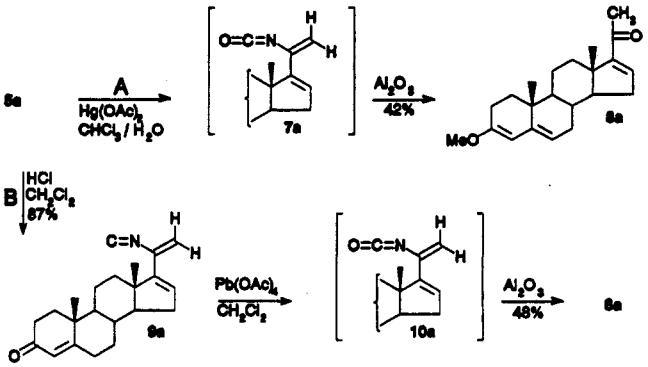
R = Me[10c,e,f,24], R = H (*i.e.* 2)[25g]

ration of compounds 5, however, is of no consequence for the hydrolysis to the C20 ketosteroids 6 to be discussed next.

α,β-Unsaturated isocyanides are essentially masked primary enamines,[1c,d] and acid hydrolysis of compounds 5 gave, as expected, a smooth and high yield, one-operational conversion to 20-ketosteroids 6 (Table II). In total, the combination of reactions of 1 with diethyl (isocyanomethyl)phosphonate (2) to 4, the Wittig–Horner–Emmons reaction to 5, and the acid hydrolysis to 6 provides a new method for the introduction of 20-ketosteroidal side chains in 17-oxosteroids (Scheme I, Tables I and II). The effectiveness of this approach is illustrated by the synthesis of 16-dehydroprogesterone (6a), using gaseous formaldehyde, in 89% overall yield from 4.

Previously, 17-oxosteroid 1 was shown to give α,β-unsaturated isocyanides 11 with diethyl (isocyanomethyl)-phosphonate (2) or with diethyl (1-isocyano*ethyl*)-phosphonate, with a double bond in C17,C20 position (Scheme II).[10c,e,f,24] Note that isocyanides 11 do not carry a phosphorus substituent, unlike compound 4. Acid hydrolysis of 11 led to 20-ketosteroids 12 (R = Me),[10c,e,f] or to 17-formylsteroids 12 (R = H),[25g] in a process related to the reaction of 5 to 6. This means that 17-oxosteroids (1) may be converted into 20-ketosteroids by either the method of Scheme I or of Scheme II. In both methods an (isocyanomethyl)phosphonate molecule fulfills the role of connective reagent between 1 and a side chain precursor, and in both methods a Wittig–Horner–Emmons reaction is used to form one of the two carbon–carbon bonds to the connective reagent. In the approach of Scheme II the future side chain first is linked to the connective reagent, through the synthesis of (1-isocyano*ethyl*)phosphonate, whereas in the method of Scheme I the side chain is introduced in the final stage of the overall process.

Scheme III



The acid hydrolysis of 5 to 6 is assumed to proceed *via* α,β-unsaturated formamides (enamides), which are formed by acid-catalyzed hydration of the isocyano group, followed by hydrolysis of these enamides. The hydrolysis of 5 to 6 was carried out with 20% aqueous H_2SO_4 in refluxing THF. Under these conditions the 3,5-dienol ether protection of the steroid A-ring is concomitantly removed to give the 4-en-3-one group.

Removal of the dienol ether protection of the enone function of the A-ring is not always desirable. As a matter of fact, the fairly acidic conditions for the hydrolysis of 5 to 6 may form a disadvantage, since acid-sensitive groups other than the dienol ether could be affected also. When such groups are present, the alternative routes depicted in Scheme III may be of use. The use of acid in the synthesis of 6 is avoided by the oxidation of isocyanide 5a to isocyanate 7a (or 9a to 10a) followed by a smooth conversion to the desired 17-acetyl steroids 8a (or 6a) by treatment with alumina. This mild conversion is assumed to occur by moisture present on the alumina to transform 7a (or 10a) to a carbamic acid followed by loss of CO_2 and hydrolysis of an enamine. The oxidations to isocyanates 7a and 10a were carried out with $Hg(OAc)_2$[26] and with $Pb(OAc)_4$,[27] respectively. With $Pb(OAc)_4$ it was necessary to first deprotect the A-ring of 5a (by mild acid hydrolysis!) to form 9a because otherwise the reaction is accompanied by oxidation of the dienol ether function (Scheme III, route B). Oxidation of 5a with $Hg(OAc)_2$ in a two-phase $CHCl_3$/H_2O system, however, was sufficiently mild to leave the dienol ether group unaffected, providing 7a, which by hydrolytic conversion on alumina gave 8a in an overall yield of 42% based on 5a (Scheme III, route A).

With the foregoing we have established that compound 4 is a useful intermediate in the formation of α,β-

(24) Because of the additional methyl group in diethyl isocyano*ethyl*phosphonate no Knoevenagel-type condensation products like 4 can be formed with ketones or aldehydes, as is the case with diethyl isocyano*methyl*phosphonate (2, Scheme I). A mechanistic rationale of the (overall) elimination of one molecule of water in the formation of 4 from 2 is given in our previous paper of this series.[1a] It should be realized, however, that isocyanide 2 is perfectly capable of forming both Knoevenagel-type condensation products (such as 4) as well as Wittig–Horner–Emmons-type products (such as 11, R = H). As a matter of fact, many examples of the latter process have been reported earlier.[1c,d,25] Our previous paper of this series[1a] describes a method for the specific formation of Knoevenagel-type condensation products like 4, based on the use of *t*-BuOK or KH in CH_2Cl_2. The outcome of these reactions, 4 or 11 (R = H), is strongly dependent on the choice of the base/solvent system.[1,25] A reasonable explanation of this apparent dichotomy has not been put forward; one highly speculative attempt has been made by one of us.[25g]

(25) (a) Schöllkopf, U.; Schröder, R. *Tetrahedron Lett.* **1973**, *9*, 633. (b) Hoppe, D. *Angew. Chem.* **1974**, *86*, 878. (c) Schöllkopf, U.; Schröder, R.; Stafforst, D. *Liebigs Ann. Chem.* **1974**, 44. (d) Rachon, J. *Chimia* **1982**, *36*, 462. (e) Schöllkopf, U.; Wintel, T. *Synthesis* **1984**, 1033. (f) Schöllkopf, U.; Hoppe, I. *Liebigs Ann. Chem.* **1984**, 600. (g) Stoelwinder, J. Ph.D. Thesis, Groningen University, The Netherlands, 1992.

(26) (a) Herdeis, C.; Nagel, U. *Heterocycles* **1983**, *20*, 2163. (b) Herdeis, C.; Dimmerling, A. *Arch. Pharm.* **1984**, *317*, 86.

(27) van Leusen, D. Ph.D. Thesis Groningen University, The Netherlands, 1990.

unsaturated isocyanosteroids (**5a-f**). The high yield acid hydrolysis to Δ^{16}-20-ketosteroids (**6a-f**) is the method of choice when the system tolerates the acidic conditions needed for isocyanide hydrolysis (Scheme I and Table II). The oxidative methods of Scheme III (of which route A uses essentially neutral conditions) provide an alternative (albeit with lower yields) when acid-sensitive functional groups are to be maintained.

Experimental Section

All aldehydes and acetone (Table I) were dried and purified by distillation prior to use. The synthesis of **5a-f** and **10a** were performed in a N_2 atmosphere. Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 MHz (unless stated otherwise); peak integrations (not reported explicitly) are consistent with the given assignments; however, it is indicated when individual peak integration was not feasible; C(18)H_3 and C(19)H_3 assignments are not always unambiguous. APT ^{13}C NMR spectra were recorded in $CDCl_3$ at 75.43 MHz; downward CH and CH_3 signals are reported as (-) chemical shifts; assignments are given for the sp^2 carbons only; C(5) and the isocyano carbon of compds **5** gave weak signals, which were not observed in all cases; assignments within the pairs of carbons C(17),C(20) and C(4),C(6) are somewhat ambiguous. Whenever possible, purification of products and intermediates was achieved by crystallization and followed by microanalysis. Otherwise, intermediates were purified by column chromatography and followed by HRMS. Formation of products **5** was monitored easily by TLC (Al_2O_3, CH_2Cl_2; $R_f \approx 0.9$), and the *E,Z*-ratios of **5b,c,e**, and **f** were determined by ^{1}H NMR. The isocyanatosteroids **7a** and **10a** were not obtained in pure form. IR spectroscopy, however, clearly indicated the absence of the isocyano group and the presence of a strong isocyanate absorption at 2256 and 2261 cm^{-1}, respectively. As was already reported by Hoppe *et al.*[25f] for similar unsaturated isocyanides, compounds **5a-f** and **9a** are unstable and are storable for some time only in crystalline form at low temperatures.

20-Isocyano-3-methoxypregna-3,5,16,20-tetraene (5a). *t*-BuOK (0.22 g, 2.0 mmol) was added to a solution of (*E*)-17-[(diethylphosphono)isocyanomethylene]-3-methoxyandrosta-3,5-diene[1a] (**4**, 0.46 g, 1.0 mmol) in THF (25 mL) at -30 °C. After the solution was stirred for 10 min, gaseous formaldehyde[28] (from 2.5 g of paraformaldehyde, large excess) was carried into the solution with a stream of nitrogen, at such a rate that the temperature was kept below -20 °C. Stirring was continued for 30 min at -20 °C, and then the temperature was raised to 0 °C. Water (20 mL) was added, and the suspension was filtered over a short column of Celite. The filtrate was extracted with Et_2O (3 × 25 mL), and after drying (Na_2SO_4) the solvents were removed to give 0.34 g of crude **5a**. The crude material was purified by filtration over a short column of Al_2O_3 (neutral, act. II/III; CH_2Cl_2) to give 0.32 g (96%) of **5a** as colorless crystals. Analytically pure **5a** was obtained by one crystallization from CH_2Cl_2/MeOH: mp 152–153 °C; IR (neat) 2123 (N≡C), 1650, 1614 cm^{-1} (C=C); ^{1}H NMR δ 0.98 (s, C(19)H_3), 1.01 (s, C(18)H_3), 1.0–2.4 (m), 3.57 (s, CH_3O), 5.14 (s, C(4)*H*), 5.25 (m, C(6)*H*), 5.33 (br s, C(21)H_2), 6.22 (m, C(16)*H*), ^{13}C NMR δ 155.3 (*C*3), 146.5 (*C*17), 142.8 (*C*5), 141.0 (*C*20), (-)134.0 (*C*16), (-)117.6 (*C*4), 112.5 (*C*21), (-)98.4 (*C*6), (-)57.7, (-)54.2, (-)48.2, 46.1, 35.2, 35.1, 33.6, 31.1, 30.8, (-)30.1, 25.1, 20.9, (-)18.7, (-)15.6; exact mass calcd for $C_{23}H_{29}NO$ *m/e* 335.226, found 335.225. Anal. Calcd for $C_{23}H_{29}NO$ (335.49): C, 82.34; H, 8.71; N, 4.18. Found: C, 81.78; H, 8.67; N, 4.10.

(20*E*)- and (20*Z*)-20-Isocyano-3-methoxy-21-methylpregna-3,5,16,20-tetraene (5b). *t*-BuOK (0.11 g, 1.0 mmol) was added to a solution of **4**[1a] (0.46 g, 1.0 mmol) in THF (25 mL) at -30 °C. After the solution was stirred for 10 min, liquid acetaldehyde[29] (0.088 g, 2.0 mmol) in THF (1 mL) was added and stirring was continued for 30 min at -20 °C. Then the temperature was raised to 0 °C and water was added. The mixture was extracted with Et_2O (3 × 25 mL) and after drying (Na_2SO_4) the solvents were removed to give 0.35 g of crude product. The crude material was purified by filtration over a short column of Al_2O_3 (neutral, act. II/III; CH_2Cl_2) to give 0.34 g (96%) of **5b** as a partially crystallizing oil, in an *E,Z*-ratio of 14:86. Analytically pure (*Z*)-**5b** (0.13 g) was obtained by two crystallizations from CH_2Cl_2/MeOH: mp 152–156 °C dec; IR (Nujol) 2116, (N≡C), 1653, 1627 cm^{-1} (C=C); ^{1}H NMR (*E,Z*-mixture) δ 0.95 (s, C(19)-H_3), 0.98 (s, C(18)H_3), 1.90 (d, *J* = 9 Hz, *ca.* 3H, C(22)H_3), 1.0–2.3 (m), 3.55 (s, CH_3O), 5.10 (s, C(4)*H*), 5.20 (m, C(6)*H*), 5.85 (m, C(21)*H*), 5.74 (m) plus 6.01 (m, C(16)*H*, *E* and *Z*-isomers, respectively, ratio. *ca.* 14:86); ^{13}C NMR ((*Z*)-**5b**) δ 163.7 (N≡*C*), 155.2 (*C*3), 146.8 (*C*17), 141.0 (*C*5,*C*20), (-)130.7 (*C*16), (-)123.8 (*C*21), (-)117.7 (*C*4), (-)98.4 (*C*6), (-)57.8, (-)54.2, (-)48.3, 46.2, 35.4, 35.2, 33.6, 31.6, 31.2, 30.7, (-)30.1, 25.2, 21.0, (-)18.8, (-)-15.8, (-)14.4; exact mass calcd for $C_{24}H_{31}NO$ *m/e* 349.241, found 349.241. Anal. Calcd for $C_{24}H_{31}NO$ (349.52): C, 82.47; H, 8.94; N, 4.01. Found: C, 81.73; H, 8.94; N, 4.24.

(20*E*)- and (20*Z*)-20-isocyano-3-methoxy-21,27-dinorcholesta-3,5,16,20-tetraene (5c) was prepared according to the procedure given for **5b**, using **4** (0.46 g, 1.0 mmol) and valeraldehyde (pentanal, 0.086 g, 1.0 mmol). Workup resulted in 0.32 g (81%) of **5c**, as a partially crystallizing oil, in an *E,Z*-ratio of *ca.* 7:93. Analytically pure (*Z*)-**5c** (0.14 g) was obtained by one crystallization from CH_2Cl_2/MeOH: mp 91–101 °C; IR (neat) 2112 (N≡C), 1653, 1628 cm^{-1} (C=C); ^{1}H NMR (*E,Z*-mixture) δ 0.93 (t, *J* = 7 Hz, C(26)H_3), 0.97 (s, C(19)H_3), 1.06 (s, C(18)H_3, *Z*-isomer), 1.13 (s, C(18)H_3, *E*-isomer), (9H altogether for peaks between δ 0.9 and 1.1), 1.1–2.4 (m), 3.59 (s, CH_3O), 5.16 (s, C(4)-*H*), 5.27 (m, C(6)*H*), 5.75 (m, C(16)*H*, *E*-isomer), 5.80 (t, *J* = 9 Hz, C(22)*H*, *Z*-isomer), 5.96 (t, *J* = 9 Hz, C(22)*H*, *E*-isomer) 6.06 (m, C(16)*H*, *Z*-isomer), (2H altogether for peaks between δ 5.7 and 6.1); exact mass calcd for $C_{27}H_{37}NO$ *m/e* 391.287, found 391.287. Anal. Calcd for $C_{27}H_{37}NO$ (391.60): C, 82.81; H, 9.52; N, 3.58. Found: C, 81.72; H, 9.71; N, 3.74.

21,21-Dimethyl-20-isocyano-3-methoxypregna-3,5,16,20-tetraene (5d) was prepared according to the procedure given for **5b**, using **4** (0.46 g, 1.0 mmol) and acetone (0.12 g, 2.0 mmol). After workup and purification by crystallization from CH_2Cl_2/MeOH, 0.32 g (87%) of **5d** was obtained as colorless crystals: mp 158–159 °C; IR (neat) 2112 (N≡C), 1654, 1629 cm^{-1} (C=C); ^{1}H NMR δ 1.01 (s, C(19)H_3), 1.03 (s, C(18)H_3), 1.82 (s, *ca.* 3H, C(22)-H_3), 2.00 (s, *ca.* 3H, C(23)H_3), 1.1–2.4 (m), 3.59 (s, CH_3O), 5.15 (s, C(4)*H*), 5.26 (m, C(6)*H*), 5.67 (m, C(16)*H*); ^{13}C NMR δ 155.4 (*C*3), 146.3 (*C*17), 141.2 (*C*5), 138.3 (C20), (-)132.7 (*C*16), (-)-117.8 (*C*4), (-)98.5 (*C*6), (-)57.4, (-)54.3, (-)48.6, 48.1, 35.4, 34.5, 33.7, 31.7, 31.4, (-)30.4, 25.3, (-)21.4, 20.8, (-)20.7, (-)18.9, (-)-16.1; exact mass calcd for $C_{25}H_{33}NO$ *m/e* 363.255, found 363.256. Anal. Calcd for $C_{25}H_{33}NO$ (363.55): C, 82.60; H, 9.15; N, 3.85. Found: C, 82.16; H, 9.15; N, 3.78.

(20*E*)- and (20*Z*)-ethyl 20-isocyano-3-methoxy-21,26,27-trinorcholesta-3,5,16,20-tetraen-25-oate (5e) was prepared analogously to the procedure given for **5b**, using **4** (0.46 g, 1.0 mmol) and ethyl 4-oxobutanoate[30] (0.13 g 1.0 mmol). Workup resulted in 0.31 g (71%) of **5e**, as a slowly solidifying unstable oil, in an *E,Z*-ratio of *ca.* 13:87: IR (neat) 2116 (N≡C), 1734 (CO_2Et), 1628, 1653 cm^{-1} (C=C); ^{1}H NMR (*E,Z*-mixture) δ 0.90 (s, C(19)H_3), 0.96 (s, C(18)H_3), 1.22 (t, *J* = 6 Hz, CH_2CH_3), 1.4-2.7 (m), 3.55 (s, CH_3O), 4.10 (q, J = 6 Hz, CH_2CH_3), 5.10 (s, C(4)*H*), 5.19 (m, C(6)*H*), 5.75 (m, C(16)*H*, *E*-isomer), 5.82 (t, *J* = 8 Hz, C(22)*H*, *Z*-isomer), 5.90 (t, *J* = 8 Hz, C(22)*H*, *E*-isomer), 6.07 (m, C(16)*H*, *Z*-isomer), (2H altogether for peaks between δ 5.7 and 6.1); ^{13}C NMR δ 172.1 (*C*=O), 164.4 (N≡*C*), 155.1 (*C*3), 146.4 (*C*17), 140.8 (C20), (-)131.6 (C16), (-)126.6 (C22), (-)117.6 (*C*4), (-)98.3 (*C*6), 60.5, (-)57.7, (-)54.1, (-)48.2, 46.1, 35.2, 35.1, 33.5, 32.9, 31.1, 30.7, (-)30.1, 25.1, 24.1, 20.9, (-)18.7, (-)15.7, (-)14.1; exact mass calcd for $C_{28}H_{37}NO_3$ *m/e* 435.277, found 435.277.

(20*E*,23*E*)- and (20*Z*,23*E*)-20-isocyano-3-methoxy-26a-homo-21,27-dinorcholesta-3,5,16,20,23-pentaene (5f) was prepared analogously to the procedure given for **5b**, at -50 °C, using **4** (0.51 g, 1.1 mmol) and a solution of (*E*)-2-hexenal (0.11 g, 1.1 mmol) in THF (10 mL). Workup resulted in 0.37 g (83%) of **5f** as a white solid, in an *E,Z*-ratio of *ca.* 9:91. Analytically pure

(28) Generated by thermolysis of paraformaldehyde: Vogel, A. I. *Textbook of Practical Organic Chemistry*, 4th ed.; Longman: London, 1978; p 293.

(29) The use of gaseous acetaldehyde, in the same way as described for **5a** with formaldehyde, gave a comparable yield of **5b**.

(30) Herdewijn, P.; Claes, P. J.; Vanderhaeghe, H. *J. Med. Chem.* **1986**, *29*, 661.

(*Z*)-**5f** (0.25 g) was obtained by crystallization from CH_2Cl_2/MeOH: mp 120–125 °C dec; IR (neat) 2110 (N=C), 1629, 1652 cm^{-1} (C=C); ^1H NMR (*E,Z*-mixture) δ 0.96 (t, J = 6 Hz, C(26a)-H_3), 0.98 (s, C(19)H_3), 1.01 (s, C(18)H_3), (9H altogether for peaks between δ 0.9 and 1.0), 1.04–2.40 (m), 3.56 (s, CH_3O), 5.15 (s, C(4)*H*), 5.25 (br s, C(6)*H*), 5.96 (br s, C(16)*H*, *E*-isomer), 5.98–6.05 (m, C(24)*H*), 6.14 (br s, C(16)*H*, *Z*-isomer), 6.29 (d, J = 11 Hz, C(22)*H*), 6.45–6.53 (m, C(23)*H*), (4H altogether for peaks between δ 5.9 and 6.6); exact mass calcd for $C_{28}H_{37}NO$ *m/e* 403.287, found 403.287. Anal. Calcd for $C_{28}H_{37}NO$ (403.61): C, 83.32; H, 9.24; N, 3.47. Found: C, 82.74; H, 9.15; N, 3.79.

Pregna-4,16-diene-3,20-dione (16-Dehydroprogesterone, 6a). According to Scheme I, Route A. An aqueous solution of 20% H_2SO_4 (1 mL) was added to a stirred solution of **5a** (0.34 g, 1.0 mmol) in THF (10 mL). The mixture was refluxed for 2 h, after which a saturated aqueous solution of Na_2CO_3 (2 mL) was added. After addition of 25 mL of water, extraction with Et_2O (3 × 25 mL), and drying (Na_2SO_4), the solvents were removed to give 0.31 g of crude product. The crude material was purified by filtration over a short column of Al_2O_3 (neutral, act. II/III; CH_2Cl_2), followed by one crystallization from Et_2O/Me_2CO to give 0.29 g (93%) of **6a** as colorless crystals: mp 185–187 °C; $[\alpha]^{20}_D$ +156° (*c* 1, EtOH) [lit.[31] mp 186–188 °C, $[\alpha]_D$ + 155° (*c* 1, EtOH)]. This material was identical with a commercial sample according to IR and ^1H NMR.

According to Scheme III, Route B. $Pb(OAc)_4$ (0.44 g, 1.0 mmol) was added to a stirred solution of **9a** (0.26 g, 0.81 mmol) in CH_2Cl_2 (5 mL), and the suspension was stirred for 1 h at 20 °C. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (15 mL). The water layer was extracted with CH_2Cl_2 (5 mL), and the combined organic layers were dried (Na_2SO_4). Then Al_2O_3 (15 g, neutral, act. II/III) was added to the organic solution, and the suspension was stirred for 4 h at 20 °C and filtered. The Al_2O_3 was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic fractions were concentrated to give 0.12 g of **6a** (48%) as colorless crystals: mp 186–187 °C; $[\alpha]^{20}_D$ +155° (*c* 1, EtOH). This material was identical with the above sample according to IR and ^1H NMR.

21-Methylpregna-4,16-diene-3,20-dione (6b) was prepared according to the procedure given for **6a** (Scheme I), from the *E/Z*-mixture of **5b** (0.29 g, 0.82 mmol). Crude **6b** (0.29 g) was purified analogously to **6a**. Crystallization from Et_2O gave analytically pure **6b** (0.257 g, 96%): mp 158–159 °C; $[\alpha]^{20}_D$ +168° (*c* 1, $CHCl_3$) [lit.[27] mp 159–160 °C, $[\alpha]_D$ +168° (*c* 1, CH_2Cl_2)]; IR ($CHCl_3$) 1663 (C=O), 1614 cm^{-1} (C=C); ^1H NMR δ 0.90 (s, C(19)-H_3), 1.03 (t, J = 6 Hz, C(22)H_3), 1.17 (s, C(18)H_3), 1.2–2.7 (m), 5.69 (s, C(4)*H*), 6.65 (s, C(16)*H*); ^{13}C NMR δ 199.4 (*C*20), 199.2 (*C*3), 170.7 (*C*5), 154.2 (*C*17), (–)142.2 (*C*16), (–)123.7 (*C*4), (–)-55.3, (–)53.8, 45.9, 38.4, 35.2, 34.2, 33.6, (–)33.5, 32.4, 31.9, 31.8, 31.5, 20.5, (–)16.9, (–)15.6, (–)8.0. Anal. Calcd for $C_{22}H_{30}O_2$ (326.483): C, 80.94; H. 9.26. Found: C, 80.84; H, 9.31.

21,27-Dinorcholesta-4,16-diene-3,20-dione (6c) was prepared according to the procedure given for **6a** (Scheme I), from the *E/Z* mixture of **5c** (0.77 g, 0.7 mmol). Crude **6c** (0.28 g) was purified analogously to **6a**. Crystallization from Et_2O–petroleum ether, bp 40–60 °C, gave analytically pure **6c** (0.216 g, 85%): mp 120–121 °C; $[\alpha]^{20}_D$ +130° (*c* 1, $CHCl_3$); IR (neat) 1669 (C=O), 1619 cm^{-1} (C=C); ^1H NMR δ 0.87 (t, J = 6 Hz, C(26)H_3), 0.93 (s, C(19)H_3), 1.20 (s, *ca.* 3H, C(18)H_3), 2.56 (t, J = 6 Hz, C(22)H_2), 5.70 (s, C(4)*H*), 6.66 (br s, C(16)*H*); ^{13}C NMR δ 199.4 (*C*20), 199.3 (*C*3), 170.8 (*C*5), 154.7 (*C*17), (–)142.5 (*C*16), (–)123.9 (*C*4), (–)-55.5, (–)54.0, 46.1, 39.1, 38.6, 35.4, 34.4, 33.8, (–)33.7, 32.6, 32.0, 31.7, 31.4, 24.2, 22.4, 20.7, (–)17.1, (–)15.7, (–)13.8. Anal. Calcd for $C_{25}H_{36}O_2$ (368.56): C, 81.47; H, 9.85. Found: C, 80.89; H, 9.82.

21,21-Dimethylpregna-4,16-diene-3,20-dione (6d) was prepared according to the procedure given for **6a** (Scheme I) from **5d** (0.22 g, 0.61 mmol). Crude **6d** (0.20 g) was purified analogously to **6a**. Crystallization from Et_2O–petroleum ether, bp 40–60 °C, gave analytically pure **6d** (0.19 g, 93%): mp 145–147 °C; $[\alpha]^{20}_D$ +145° (*c* 1, $CHCl_3$); IR (neat) 1662 (C=O), 1608 cm^{-1} (C=C); ^1H NMR δ 0.90 (s, C(19)H_3), 1.02 (dd, J_1 = J_2 = 6 Hz, C(22)H_3, C(23)H_3), 1.17 (s, C(18)H_3), 1.2–2.5 (m), 3.08 (m, C(21)*H*), 5.70 (s, C(4)*H*), 6.63 (br s, C(16)*H*); ^{13}C NMR δ 203.4 (*C*20), 199.3 (*C*3), 170.8 (*C*5), 153.5 (*C*17), (–)142.0 (*C*16), (–)123.7 (*C*4), (–)-55.3, (–)53.9, 46.0, 38.5, (–)36.1, 35.4, 34.2, 33.7, (–)33.6, 32.5, 31.9, 31.6, 20.6, (–)19.5, (–)18.6, (–)17.0, (–)15.6. Anal. Calcd for $C_{23}H_{32}O_2$ (340.51): C, 81.13; H, 9.47. Found: C, 80.90; H, 9.33.

Ethyl 3,20-dioxo-21,26,27-trinorcholesta-4,16-dien-25-oate (6e) was prepared according to the procedure given for **6a** (Scheme I) from **5e** (0.39 g, 0.90 mmol). Crude **6e** (0.26 g, 69%) was purified analogously to **6a**. Crystallization from Et_2O-petroleum ether, bp 40–60 °C, gave analytically pure **6e** (0.16 g, 43%): mp 97–98 °C; $[\alpha]^{20}_D$ + 126° (*c* 1, $CHCl_3$); IR (neat) 1732 (CO_2Et), 1665 cm^{-1} (C=O); ^1H NMR δ 0.92 (s, C(19)H_3), 1.19 (s, *ca.* 3H, C(18)H_3), 1.23 (t, J = 7 Hz, *ca.* 3H, CH_2CH_3), 2.64 (m, C(22)H_2), 1.0–2.5 (m), 4.10 (q, J = 7 Hz, CH_2CH_3), 5.72 (s, C(4)*H*), 6.69 (br s, C(16)*H*). Anal. Calcd for $C_{26}H_{36}O_4$ (412.57): C, 75.69; H, 8.80. Found: C, 75.50; H, 8.97.

(23*E*)-26a-Homo-21,27-dinorcholesta-4,16,23-triene-3,20-dione (6f) was prepared according to the procedure given for **6a** (Scheme I) from the *E/Z* mixture of **5f** (0.20 g, 0.50 mmol). Crude **6f** (0.182 g) was purified analogously to **6a**. Crystallization from Et_2O–petroleum ether, bp 40–60 °C, gave analytically pure **6f** (0.17 g, 89%): mp 98–100 °C; $[\alpha]^{20}_D$ +126° (*c* 1, $CHCl_3$); IR (neat) 1674 (C=O), 1615 cm^{-1} (C=C); ^1H NMR δ 0.87 (t, J = 7 Hz, C(26a)H_3), 0.93 (s, C(19)H_3), 1.20 (s, *ca.* 3H, C(18)H_3), (6H altogether for peaks between δ 0.9 and 1.0), 1.0–2.5 (m), 3.31 (m, C(22)H_2), 5.51 (m, C(23)*H* + C(24)*H*), 5.73 (br s, C(4)*H*), 6.69 (m, C(16)*H*); ^{13}C NMR δ 199.3 (*C*3), 197.1 (*C*20), 170.7 (*C*5), 154.2 (*C*17), (–)143.2 (*C*16), (–)134.1, (–)123.8 (*C*4), (–)122.7, (–)55.4, (–)53.9, 46.1, 43.0, 38.5, 35.4, 34.5, 34.2, 33.8, (–)33.7, 32.5, 32.0, 31.6, 22.2, 20.6, (–)17.0, (–)15.6, (–)13.5. Anal. Calcd for $C_{26}H_{36}O_2$ (380.58): C, 82.06; H, 9.53. Found: C, 81.67; H, 9.74.

3-Methoxypregna-3,5,16-trien-20-one (8a). Scheme III, Route A. To a stirred solution of **5a** (0.17 g, 0.50 mmol) in $CHCl_3$ (10 mL) was added a solution of $Hg(OAc)_2$ (0.17 g, 5.33 mmol) in water (10 mL). Stirring was continued for 1 h at 20 °C. The mixture was diluted with $CHCl_3$ (15 mL) and washed with water (15 mL). The water layer was extracted once with $CHCl_3$ (15 mL), and the combined organic layers were dried with a mixture of Na_2SO_4 and zinc powder.[32] Then, the filtrate was stirred for 4 h at 20 °C with Al_2O_3 (15 g, neutral, act. II/III) and filtered. The Al_2O_3 was extracted with $CHCl_3$ (2 × 25 mL). The combined organic layers were concentrated to give 0.089 g of crude **8a** as colorless crystals. The crude material was purified by filtration over a short column of Al_2O_3 (neutral, act. II/III; CH_2Cl_2) followed by one crystallization from Me_2CO/MeOH with a trace of NEt_3 to give 0.69 g (42%) of **8a**: mp 150–157 °C [lit.[15] mp 152–167 °C]; IR (neat) 1667 (C=O), 1654, 1627 cm^{-1} (C=C); ^1H NMR (200 MHz) δ 0.87 (s, C(19)H_3), 0.95 (s, C(18)H_3), 2.20 (s, C(21)H_3), 3.52 (s, CH_3O), 5.05 (s, C(4)*H*), 5.16 (m, C(6)*H*), 6.65 (m, C(16)*H*).

20-Isocyanopregna-4,16,20-trien-3-one (9a). Scheme III, Route B. Five drops of 2 N HCl were added to a stirred solution of **5a** (0.34 g, 1.00 mmol) in CH_2Cl_2 (5 mL) to deprotect the steroid A-ring. The mixture was stirred for 2 h at 20 °C, after which it was filtered over a thin layer of Na_2SO_4. The solvents were removed to give 0.30 g of crude product. The crude material was purified by filtration over a short column of Al_2O_3 (neutral, act. II/III; CH_2Cl_2) to give 0.28 g (87%) of **9a** as colorless crystals. Analytically pure **9a** was obtained by one crystallization from CH_2Cl_2/MeOH: mp 171 °C dec; IR (neat) 2122 (N=C), 1663 (C=O), 1616 cm^{-1} (C=C); ^1H NMR δ 0.98 (s, C(19)H_3), 1.18 (s, C(18)H_3), 1.0–2.5 (m), 5.74 (s, C(4)*H*), 5.17 (br s, C(21)H_2), 6.20 (m, C(16)*H*); exact mass calcd for $C_{22}H_{27}NO$ *m/e* 321.209, found 321.209. Anal. Calcd for $C_{22}H_{27}NO$ (321.47): C, 82.20; H, 8.47; N, 4.36. Found: C, 81.71; H, 8.40; N, 4.0.

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(31) Wettstein, A. *Helv. Chim. Acta* **1944**, *27*, 1803.

(32) Zinc (powder) was used to remove traces of mercury from the solution.